Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=OR			
L20	L19 and insulin	32	L20
L19	L18 and nasal	43	L19
L18	porous and hydroxyapatite and powder	844	L18
L17	porous and hydroxyapatite and (powder or nasal)	872	L17
L16	porous and hydoxyapatite and powder	13	L16
DB=JPAB; PLUR=YES; OP=OR			
L15	porous adj1 calcium adj1 carbonate and nasal	0	L15
DB=USPT; PLUR=YES; OP=OR			
L14	porous adj1 calcium adj1 carbonate and nasal	0	L14
L13	porous adj1 particles and hydroxyapatite and nasal	17	L13
L12	porous adj1 hydroxyapatite and nasal	8	L12
L11	hydroxyapatite and porous adj1 particles and nasal	17	L11
L10	hydroxyapatite and calcium adj1 carbonate and porous adj1 particles and nasal	11	L10
L9	hydroxyapatite and calcium adj1 carbonate and porous adj1 particles	30	L9
L8	hydroxyapatite and porous adj1 particle$ and nasal	17	L8
L7	hydroxyapatite and porous particle and nasal	7354	L7
L6	porous adj3 calcium adj1 carbonate and hyperglycemia	0	L6
L5	L2 and nasal adj1 administr$	0	L5
L4	L2 and diabetes	1	L4
L3	L2 and insulin	1	L3
L2	porous adj3 calcium adj1 carbonate	62	L2
L1	diabetes and insulin and porous adj1 calcium adj1 carbonate	0	L1

END OF SEARCH HISTORY

Porous adj

WEST Search History

DATE: Monday, July 15, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L8	L7 and nasal$	14	L8
L7	L6 and (calcium adj1 carbonate)	62	L7
L6	L2 and insulin	436	L6
L5	L4 and insulin	14	L5
L4	L3 and (calcium adj1 carbonate)	30	L4
L3	L2 and nasal$	124	L3
L2	porous adj10 (microparticle$ or microsphere$ or particles)	22163	L2
L1	porous adj10 nasal$	19	L1

END OF SEARCH HISTORY

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L7: Entry 34 of 62 File: USPT

DOCUMENT-IDENTIFIER: US 5916597 A
TITLE: Composition and method using solid-phase particles for sustained in vivo release of a biologically active agent

Detailed Description Text (3):
A biologically active agent, as defined herein, is an agent, or its pharmaceutically acceptable salt, which possesses therapeutic, prophylactic or diagnostic properties in vivo. Examples of suitable therapeutic and/or prophylactic biologically active agents include, for instance, proteins such as immunoglobulin-like proteins, antibodies, cytokines (e.g., lymphokines, monokines, chemokines), interleukins, interferons, erythropoietin, nucleases, tumor necrosis factor, colony stimulating factors, insulin, enzymes, tumor suppressors, hormones (e.g., growth hormone and adrenocorticotrophic hormone), antigens (e.g., bacterial and viral antigens), growth factors; peptides; polypeptides; nucleic acids such as antisense molecules; and small molecules such as antibiotics, steroids, decongestants, neuroactive agents, anesthetics, sedatives, anti-tumor agents, cardiovascular agents, antineoplastics, antihistamines, hormones and vitamins.

Detailed Description Text (17):
In an alternative embodiment, the biologically active agent is encapsulated in a lipid-based solid-phase material, such as waxes, or in a bioceramic material. Examples of suitable bioceramic materials include alumina, zirconium, calcium phosphate, calcium carbonate, zinc-calcium phosphorus oxide, zinc sulfate-calcium phosphate, ferric calcium phosphorus oxide, hydroxyapatite and aluminum oxide.

Detailed Description Text (32):
Examples of suitable sources of multivalent metal cations include, or contain, for example, magnesium hydroxide, magnesium carbonate, calcium carbonate, zinc carbonate, magnesium acetate, zinc acetate, magnesium sulfate, zinc sulfate, magnesium chloride, zinc chloride, zinc citrate, magnesium citrate and combinations thereof.

Other Reference Publication (3):
Costantino, H. R., et al., "Moisture-Induced Aggregation of Lyophilized Insulin," Pharmaceutical Research, 11(1): 21-29 (1994).

Other Reference Publication (7):
Sato, Toyomi, et al., "Porous Biodegradable Microspheres for Controlled Drug Delivery. I. Assessment of Processing Conditions and Solvent Removal Techniques," Pharmaceutical Research, 5(1): 21-29 (1988).

L7: Entry 61 of 62 File: USPT

DOCUMENT-IDENTIFIER: US 4780422 A
TITLE: Dyed inorganic composite particles and process for production thereof

Detailed Description Text (17):
Carbonates of metals such as calcium carbonate and magnesium carbonate and sulfates of metals such as barium sulfate and strontium sulfate may also be used as the inorganic compound constituting the core. Silica, alumina, titania, zirconia and compound oxides comprising them as main components are most preferably used in this invention as the inorganic compound constituting the core. These metal oxides or compound oxides are known compounds, and there is no particular restriction on the method of their production. These compounds may be produced typically by using, or substantially following, the methods described in, for example, Journal of Colloid and Interface Science, 26, 62-69 (1968), Japanese Laid-Open Patent Publication No. 138094/1977, and British Patent No. 2,115,799. Typical examples of the compound oxides are composed of silica and at least one oxide of a metal selected from metals of Groups I, II, III and IV of the periodic table, generally containing at least 80 mole % of silica.

Detailed Description Text (50):
According to another aspect, the inorganic composite particles of this invention can also be produced by selecting porous particles having a mean particle diameter of 0.05 to 8 micrometers and good particle dispersibility value, for example, at least 80% as the metal oxide particles constituting the core, contacting the porous particles with a solution of a dye, and as required, forming a coated layer by the method to be described hereinafter. In this method of producing the inorganic composite particles, the selection of the porous particles is an important requirement. Although the method of producing the inorganic composite particles is not limited in particular, porous particles obtained by a method to be described are especially preferred. For example, particles of a compound oxide comprising a metal of Group III, IV or VIII of the periodic table and an alkali metal such as potassium, sodium and lithium are prepared by the hydrolysis of the aforesaid metal alkoxide. Then, the resulting compound oxide particles are brought into contact with a solution of a mineral acid such as sulfuric acid, nitric acid or hydrochloric acid to leach the alkali metal component. The resulting particles are porous and have a particle dispersibility value of at least 80%. By impregnating the resulting particles with a solution of the dye, the dye is impregnated in the surface portion of the core to form a dyed layer on the core.

Detailed Description Text (51):
In an embodiment of forming a coated layer on the porous inorganic compound particles impregnated with the dye, the porous inorganic particles are suitably as follows.

Detailed Description Text (52):
The pore size of the porous inorgnaic compound particles are not particularly limited, but the suitable pore size is generally 20 to 500 .ANG., preferably 40 to 100 .ANG.. The suitable depth of each pore is generally in the range of 1/10 to 1/2 of the mean particle diameter of the porous inorganic compound particles. The porous inorganic compound particles preferably have a mean particle diameter of 0.05 to 8.0 micrometers and a particle dispersibility value of at least 80%, particularly at least 90%.

Detailed Description Text (53):

Sometimes, the dye may dissolve out from the dyed layer composed of the dye or the mixture of the dye and the inorganic compound. To prevent the possibility of dissolution, the inorganic composite particles may be prepared in a three-layer structure by further applying a coated layer of an inorganic compound having a low dye content or containing no dye, or in a structure consisting of four or more layers by repeating the formation of the dyed layer and the coated layer. There is no particular limitation on the means of forming such a multi-layer structure, and any desired means can be utilized. A generally preferred method is, for example, a method which comprises adding dropwise the dye and the compound capable of yielding the inorganic compound by hydrolysis to a water-containing solvent in which the inorganic compound forming the core is present and hydrolyzing the compound to form particles of a two-layer structure, or preparing porous particles impregnated with the dye, and thereafter further adding dropwise the compound capable of yielding the inorganic compound by hydrolysis in the same reactor to hydrolyze it; or a method which comprises separating the unreacted materials or the non-impregnated dye from the aforesaid system of producing the two-layer particles or the dye-impregnated porous particles, and thereafter further adding the compound capable of yielding the inorganic compound by hydrolysis and hydrolyzing the compound to give inorganic composite particles. In the former case in which the reactions are carried out in the same system, composite particles of a three-layer structure are obtained. The coated layer as the third layer has a very low dye content when the dye remaining unconsumed in the formation of the dyed layer on the core is present dissolved in the solvent but the solution of the inorganic compound-yielding compound to be added contains no dye. In this case, the amount of the dye in the coated layer is usually about 1/5 or less, preferably 1/10 or less, of the weight of the dye contained in the dyed layer directly coated on the core. This phenomenon is also surprising in view of general reactions, but its mechanism has not been elucidated. Accordingly, the production of the inorganic composite particles of the invention does not require any special mode of reaction. They can be obtained also by successively laminating three or more layers in a sole reactor in situ. In the composite particles so obtained, any dye which may be contained in a small amount in the third layer hardly dissolves out.

Detailed Description Text (68):
The immunologically active substance (antigen and antibody) to be bound to the composite particles of this invention is not critical and may be any known antigen and antibody. Examples include denatured gamma-globulins, antinuclear factor, human albumin, anti-human albumin antibody, immunoglobulin G (IgG), anti-human IgG antibody, immunoglobulin A (IgA), anti-human IgA antibody, immunoglobulin M (IgM), anti-human IgM antibody, anti-human IgE antibody, streptolysin O streptokinase, hyaluronidase, C-reactive protein (CRP), anti-human CRP antibody, alpha-fetoprotein (AFP), anti-APP antibody, carcinoembryonic antigen (CEA), anti-human CEA antibody, human chorionic gonadotropin (HCG), anti-HCG antibody, anti-estrogen antibody, anti-insulin antibody, type B hepatitis surface antibody (HBs), anti-HBs antibody, treponema pallidium antigen, rubella antigen, influenza antigen, complement CIq, anti-CIq antibody, anti-C.sub.3 antibody, anti-C.sub.4 antibody and anti-transferrin antibody.

Detailed Description Text (69):
Other known biologically active substances which bind to the inorganic composite particles of this invention may also be used. Examples include enzymes such as horseradish peroxidase, glucose oxidase, superoxide dismutase, and cytochrome a, b, b.sub.1, c and p450; hormones such as pituitary hormones, insulin, glucagon and thyroid hormone; and haptens such as opium alkaloid (morphine), antipyrine and barbituric acid.

Detailed Description Text (136):
A glass flask equipped with a stirrer was charged with 2800 ml of methanol, 616 ml of aqueous ammonia (25% by weight), and 21 ml of an aqueous solution of sodium hydroxide (5 moles/liter). The flask was maintained at 10.degree. C., and then a mixture of 792 ml of a methanol solution (22% by weight) of tetraethyl silicate and 88 ml of a methanol solution (22% by weight) of sodium methylate was added dropwise at a rate of 25.5 ml to give silica/sodium composite particles. The composite particles were purified as in Example 1, (1), and dispersed in methanol to a concentration of 10% by weight. Then, 2000 ml of a 5% by weight aqueous solution of sulfuric acid was put in a glass flask equipped with a stirrer, and with stirring at room temperature, the

dispersion of the composite particles was added dropwise at a rate of 5 ml/min. After the acid treatment, the product was washed and purified in the same way as in Example 1, (1). The properties of the resulting porous particles are shown in Table 2, No. 1.

Detailed Description Text (137):
Separately, 2800 cc of isopropyl alcohol (IPA) was added to a glass flask equipped with a stirrer, and after the flask was maintained at 10.degree. C., a mixture of 855 ml of an IPA solution (20% by weight) of each of the materials shown in Table 7, (Nos. 1, 3 and 4) and 95 ml of an IPA solution (20% by weight) of sodium methylate was added dropwise at a rate of 25.5 ml to obtain silica-sodium composite particles. The composite particles were purified as in Example 1, (1), and dispersed in methanol in a concentration of 10% by weight. Then, 2000 ml of a 5% by weight aqueous solution of sulfuric acid was put in a glass flask equipped with a stirrer, and with stirring at room temperature, the dispersion of the composite particles was added dropwise at a rate of 5 ml/min. After the acid-treatment, the product was washed and purified in the same way as in Example 1, (1). The properties of the porous particles are shown in Table 7, (Nos. 1, 3 and 4).

Detailed Description Text (138):
The resulting porous particles were precipitated, and the supernatant methanol was removed. Then, 1000 ml of a methanol solution of Methylene Blue dissolved in a concentration of 10% by weight was added. The mixture was stirred at room temperature for 16 hours to impregnate the porous particles with the dye. After dyeing, the product was washed and purified in the same way as in Example 1, (1).

Detailed Description Text (139):
The dyed porous particles obtained in each of Table 7, Nos. 1 to 4 were dispersed in 100 ml of a mixture of methanol and ammonia (4:1) to a concentration of 2.5% by weight. The dispersion was taken into a glass flask equipped with a stirrer, and maintained at 10.degree. C. Thereafter, 160 ml of a methanol solution (20% by weight) of tetraethyl silicate and 160 ml of a mixture of methanol and ammonia (4:1) were simultaneously added dropwise at a rate of 22.5 ml/hr to obtain inorganic composite particles. The properties of the resulting inorganic composite particles are shown in Table 7.

Detailed Description Paragraph Table (7):
TABLE 7

Porous particles	Dyed inorganic composite particles											
Material	Mean Particle size	Particle	Mean Particle size	Particle	for the particle	dispersion	dispersibility	particle	dispersion	dispersibility	inorganic	Inorganic
diameter	value	value	diameter	value	value	No.	compound	compound	(.mu.m)	(%)	(%)	(.mu.m)	(%)	(%)		
1	Tri-sec-butyl aluminate	Alumina	2.17	6.3	93.5	2.39	7.1	91.2								
2	Tetra-ethyl silicate	Silica	1.64	5.1	95.4	1.89	6.3	92.6								
3	Tetra-n-butyl titanate	Titania	1.01	7.2	90.8	1.13	7.9	89.1								
4	Tetra-n-butyl zirconate	Zirconia	0.87	6.4	91.6	1.01	7.2	90.5								

Dyed inorganic composite particles	Immunological diagnostic reagent											
Thickness of the coated layer (.mu.m)	Particle dispersibility	Non-specific agglutination value	Proportion of the dye in the dyed layer based on the entire dye (%)	Rapidity No.	Sensitivity	(min.)	(number)					
1	97	0.22	90.1	x5120	30	0	2	98	0.25	91.5	x5120	30	0	3	99	0.12	88.6	x2560	45	0	4	99	0.14	89.3	x2560	45	0

CLAIMS:

12. The composite particles of claim 1 wherein the core is composed of porous inorganic compound particles, and the dyed layer is composed of a dye impregnated in the surface layer of the porous particles.

22. A process for producing dyed inorganic composite particles, which comprises dispersing porous inorganic compound particles impregnated with a dye in a neutral or alkaline water-containing solvent capable of dissolving a compound yielding an

inorganic compound by hydrolysis but substantially incapable of dissolving the hydrolysis product of the compound, adding dropwise the compound yielding an inorganic compound by hydrolysis to the solvent, and hydrolyzing said compound to form a coated layer on the surface of the particles.

23. The process of claim 22 wherein the porous inorganic compound particles have a mean particle diameter of 0.05 to 8 .mu.m.

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L7: Entry 20 of 62 File: USPT

DOCUMENT-IDENTIFIER: US 6254852 B1
TITLE: Porous inorganic targeted ultrasound contrast agents

Abstract Text (1):
Targeted ultrasound contrast agents are described. The contrast agents are porous particles of an inorganic material containing an entrapped gas or liquid and having an average particle diameter of about 0.05 to 500 microns. The outer surfaces of the particles incorporate a targeting ligand to target delivery of the contrast agent.

Brief Summary Text (2):
The invention relates generally to targeted ultrasound contrast agents having porous particles of an inorganic material containing an entrapped gas or liquid and having an average particle diameter of about 0.05 to 500 microns. The outer surfaces of the particles incorporate a targeting ligand to target delivery of the contrast agent.

Brief Summary Text (12):
Glajch et al, U.S. Pat. No. 5,147,631, discloses porous particles of an inorganic material containing an entrapped gas or liquid. The materials disclosed include monomeric or polymeric borates, monomeric or polymeric aluminas, monomeric or polymeric carbonates, monomeric or polymeric silicas, monomeric or polymeric phosphates; and pharmaceutically acceptable organic or inorganic cationic salts thereof.

Brief Summary Text (17):
The present invention relates to targeted ultrasound contrast agents comprising inorganic porous particles useful for ultrasound imaging and a targeting ligand that directs the particles to a body organ or disease site. Such contrast agents may be an important adjunct in ultrasound diagnostic procedures, for example, for cardiovascular, oncologic, and gastrointestinal uses. The inorganic porous particles of the invention provide contrast for ultrasound imaging; i.e., the particles act to reflect ultrasound waves and thereby enhance the ultrasound signal when introduced into the organ system being imaged using ultrasound.

Brief Summary Text (19):
The present invention provides novel targeted ultrasound contrast agents, comprising: a pharmaceutically acceptable carrier and porous particles of an inorganic material having an average particle diameter of about 0.05 to 500 microns and containing entrapped gas or liquid, and containing, on the outside surface of the particle, a targeting ligand to target delivery of the contrast agent. The entrapped gas or liquid provides a suitable echogenic interface to enhance an ultrasound image.

Brief Summary Text (20):
The targeting ligand is attached to the porous inorganic particles by coating, adsorbing, layering, or reacting the outside surface of the particle with the targeting ligand. Representative targeting ligands include RGD-containing peptides, other compounds that bind to members of the integrin, selectin, and IgG receptor superfamilies as well as cell surface substances which cause white blood cells to move towards sites of infection/inflammation, i.e., fMLF and leukotriene receptors (LTA, B, C, D.sub.4).

Brief Summary Text (21):
The porous inorganic particles of the invention may be coated with a variety of

organic polymeric and lipid materials to control the stability, pharmacokinetics, targeting, and biological effects of the particles in vivo.

Brief Summary Text (22):
The porous inorganic particles of the invention are administered parentally or nonparentally with a pharmaceutically acceptable carrier to a person, to thereby enhance the ultrasound image of a tissue or organ system of that person.

Brief Summary Text (26):
P is a porous particle of an inorganic material having an average particle diameter of about 0.05 to 500 microns and containing an entrapped gas or liquid,

Brief Summary Text (46):
[12] In another preferred embodiment the porous particles have a single pore which is entirely or partially enclosed by a shell of the inorganic material.

Brief Summary Text (48):
[14] In another preferred embodiment the porous particles have a plurality of pores which are entirely or partially enclosed by the inorganic material.

Brief Summary Text (49):
[15] In another preferred embodiment the porous particles of inorganic material have a density of less than about 90% of the density of the inorganic material in a solid non-porous state.

Brief Summary Text (50):
[16] In another more preferred embodiment the porous particles of inorganic material have a density of less than about 60% of the density of the inorganic material in a solid non-porous state.

Brief Summary Text (51):
[17] In another even more preferred embodiment the porous particles of inorganic material have a density of 0.2% to 50% of the density of the inorganic material in a solid non-porous state.

Brief Summary Text (52):
[18] In another preferred embodiment the porous particles of inorganic material are substantially spherical in shape.

Brief Summary Text (54):
[20] In another more preferred embodiment the porous particles of inorganic material are coated with an organic material.

Brief Summary Text (63):
The term phosphates, as used herein, also includes derivatives of phosphates containing additional elements. For example, nitrogen can be incorporated into phosphate glasses to form oxynitride glasses, as described by Reidmeyer et al. (1986) J. Non-crystalline Solids 85: 186-203, the teaching of which is incorporated herein by reference. Nitriding the phosphate starting glass is expected to decrease the dissolution rate of the solid in water and increase the chemical stability of the solid. The preparation of phosphorus oxynitride glass by melting sodium metaphosphate in anhydrous ammonia to produce glasses containing up to 12 wt % nitrogen is described by Reidmeyer et al. Porous particles of oxynitride glasses and crystalline solids useful in the present invention can be prepared using the methods, described below.

Brief Summary Text (64):
Silicates and silicas, as used herein, includes any and all siliceous materials in the particulate form stated above. Typical silica material includes SiO.sub.2, silicate-containing minerals, and synthetic silicates such as silica gels, powders, porous glass and those prepared by hydrolysis of calcium silicide or sodium silicate. The preparation of porous silica particles is described in Bergna and Kirkland, U.S. Pat. No. 4,131,542, Kirkland, U.S. Pat. No. 3,782,075, and Kirkland, U.S. Pat. No. 3,505,785, the contents of which are incorporated herein by reference.

Brief Summary Text (65):
The inorganic particles of the invention have the advantages of good mechanical stability and rigidity, which are important attributes lacking in other materials used as ultrasound contrast agents, such as sonicated albumin microspheres and perflurorocarbon emulsions. In addition, inorganic particles can be prepared and fabricated, using known techniques, into a variety of shapes, sizes, and extents of porosity, in order to obtain the most desirable contrast effects. In addition, inorganic porous particles can be prepared with a range of different solubilities in aqueous solution, such as a body fluid. The solubility of the inorganic porous particle may affect the rate of biodegradation and clearance of the agent in vivo and may, thereby, be an important property affecting the biological responses and toxicity associated with the ultrasound contrast agent.

Brief Summary Text (66):
The inorganic porous particles useful in the present invention comprise an inorganic solid material that encloses or partially encloses one or more pores or cavities. The porous particles of the invention contain an entrapped gas or liquid to provide a suitable echogenic interface to enhance an ultrasound image. The pore or pores may be completely enclosed or encapsulated by the inorganic material or may be partially enclosed and open to the surface of the particle. Thus, the particles are porous or hollow and contain an entrapped or partially entrapped gas or liquid in the pore or pores. Porous inorganic particles useful in this invention include particles having a single pore enclosed by a solid shell; i.e., hollow particles. Alternatively, the porous particle may have a single pore which is partially enclosed by a solid shell. The porous particles of the invention also include particles containing a plurality of pores. The pores may be interconnected and may connect to an opening at the surface of the particle. The particles may also contain pores which are completely enclosed and are not interconnected or open to the surface of the particle. Particles with non-interconnected and completely enclosed pores are known as closed cell foam type particles.

Brief Summary Text (68):
For purposes of tissue perfusion, the porous inorganic particle should preferably be about 0.2, 0.4, 0.6, 0.8, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 microns in diameter and thereby small enough to pass through capillaries, which are about 8 to 10 microns in diameter, so as to perfuse the tissue. The porous inorganic particles of the invention should be small enough to permit their passage through capillaries without being filtered out and capable of perfusing the tissue and produce an enhanced ultrasound image that is of resolution sufficient to distinguish, for example, between well perfused and poorly perfused tissue for the detection and diagnosis of ischemia.

Brief Summary Text (69):
The porous gas-containing inorganic particles of the invention should have a density that is less than about 90, 80, 70, or 60% of the density of the solid nonporous inorganic material, preferably less than 60% of the density of the solid nonporous inorganic material. The density of the gas-containing porous inorganic particles of the invention is preferably about 0.2, 0.4, 0.6, 0.8, 1, 5, 10, 20, 30, 40, or 50% of the density of the non-porous inorganic material. The pore diameter may vary depending on the size of the particle and the number of pores, to achieve the preferred particle density. Thus, the pore size may range from about 20 angstrom to 500 microns. The pore diameters may be about 20, 100, 200, 300, 500, 1000 or 2000 angstroms for porous particles having a plurality of pores. For porous particles having a single pore, the thickness of the solid shell may vary. The shell thickness may be about 1-45% of the diameter of the particle. Thus, for porous particles having a single pore (i.e., hollow particles) having a particle size of about 0.2, 1, 10, 100, 200, 300, 400, or 500 microns, the pore size may correspondingly be about 0.2, 1, 10, 100, 200, 300, 400, or 500 microns.

Brief Summary Text (70):
The porous inorganic particles typically have a specific surface area of about 1, 10, 50, 100, 200, 500, 1000, or 1500 m.sup.2 /g. Because the porous inorganic particles of the present invention are modified on or near the outer surface the effective (i.e., derivatizable) surface area includes only the outer surface of the porous particle. Thus, it is only a small portion of the specific surface area of the porous

particle. Typically, the effective surface area is less than 10 m.sup.2 /g of porous particle. The porous inorganic particles of the invention may have a gas volume per gram of particle of greater than 0.05 mL/g, and preferably about 0.05, 0.1, 1, 5, 10, 20, 30, 40, or 50 mL/g.

Brief Summary Text (71):
Porous inorganic particles of the invention, useful as ultrasound contrast agents, may be prepared using standard methods for the preparation of porous particles. For example, porous inorganic particles may be prepared using standard methods involving the spraying of a metal salt solution into a furnace at elevated temperatures, such as standard spray drying, evaporation decomposition, high temperature aerosol decomposition, or drop-generator procedures.

Brief Summary Text (72):
The spray-drying procedure, as applied for the preparation of porous silica particles is described in Bergna and Kirkland, U.S. Pat. No. 4,131,542, the teaching of which is incorporated herein by reference. Similar procedures can be used for the preparation of porous particles composed of other materials including borates, aluminates, carbonates, phosphates, and mixtures thereof.

Brief Summary Text (76):
The gas in the pore or pores of the porous inorganic particle may be a pure gas or mixture of gases, such as air. For example, elemental gases such as O.sub.2, N.sub.2, H.sub.2, He, argon, and other noble gases, and other light gases, such as CO.sub.2, CF.sub.4, or C.sub.2 F.sub.6, C.sub.3 F.sub.8, C.sub.4 F.sub.10, and other fluorocarbon gases are expected to provide useful ultrasound contrast properties. The gases may be incorporated into the pores of the particles, for example, by exchange at high temperature and/or high pressure. Preferably the perfluorocarbon have less than six carbon atoms, e.g., CF.sub.4, C.sub.2 F.sub.6, C.sub.3 F.sub.8, cyclo-C.sub.4 F.sub.8, C.sub.4 F.sub.10, C.sub.5 F.sub.12, cyclo-C.sub.5 F.sub.10, cyclo-C.sub.4 F.sub.7 (1-trifluoromethyl), propane (2-trifluoromethyl)-1,1,1,3,3,3 hexafluoro, and butane (2-trifluoromethyl)-1,1,1,3,3,3,4,4,4 nonafluoro. Also preferred are the the corresponding unsaturated versions of the above compounds, for example C.sub.2 F.sub.4, C.sub.3 F.sub.6, the isomers of C.sub.4 F.sub.8. The halogenated versions of hydrocarbons, where other halogens are used to replace F (e.g., Cl, Br, I) would also be useful, but may not be as desirable as the perfluorinated versions. Also, mixtures of these gases, especially mixtures of perfluorocarbons with other perfluorocarbons and mixtures of perfluorocarbons with other inert gases, such as air, N.sub.2, O.sub.2, He, would be useful. In addition to gases, liquids with boiling points below 37.degree. C. can also be used. Examples of these can be found in Quay, U.S. Pat. No. 5,595,723, the contents of which are herein incorporated by reference.

Brief Summary Text (77):
The porous inorganic particles useful in the present invention may have a range of solubility in aqueous solution. Porous inorganic particles of any desired solubility can be obtained in several ways. The solubility can be controlled by selection of the desired particle surface area, the particle shell thickness, and/or the type of solid used in the particle. The inorganic particles may be comprised of a relatively insoluble solid, such as silicate materials, or may be relatively soluble in aqueous solution. For example, as discussed below, the solubility of phosphate materials can be controlled by the temperature and heating time used to prepare various amorphous or crystalline forms of phosphate material.

Brief Summary Text (78):
The porous inorganic particles must have a sufficiently slow dissolution rate in aqueous solution so as to exist in vivo following administration for at least about 1-30 minutes to provide enough time for the imaging procedure to be performed. For certain imaging applications, such as cardiovascular applications, where the contrast agent is administered parenterally, it may be desirable to use particles which are relatively soluble in serum or other body fluid. Porous inorganic particles having slower dissolution rates (i.e., reduced solubility) or insoluble particles, such as silica or alumina particles, may be desired for other uses, such as gastrointestinal imaging applications.

Brief Summary Text (79):
The porous inorganic particles of the present invention are modified on or near the outer surface of the particles to include a targeting ligand, i.e., a biologically active molecule or cell adhesion molecule. The biologically active molecule can be a protein, antibody, antibody fragment, peptide or polypeptide, or peptidomimetic that is comprised of a recognition sequence or unit for a receptor or binding site expressed at the site of the disease, or for a receptor or binding site expressed on platelets or leukocytes. The exact chemical composition of the biologically active molecule is selected based on the disease state to be diagnosed, the mechanism of localization to be utilized, and to provide an optimium combination of rates of localization and clearance.

Brief Summary Text (81):
Cytokines are cellular regulatory proteins. They are produced by specific cells in response to a variety of stimuli and they can influence the behavior of target cells. They may act systemically or locally. Examples of cytokines include: Angiogenin, Epidermal growth factor, erythropoietin, Fibroblast Growth Factor (FGF), FGF basic, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), placental growth factor (PlGF), granulocyte-colony stimulating factor, granulocytemacrophage colony stimulating factor, GROa/MGSA, hepatocyte growth factor, heparin binding epidermal growth factor, interferon (IFN), IFNa/B, IFNd, insulin-like growth factor (IGF), IGF-I, IGF-II, interleukin (IL), IL-1a, IL-1b, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, and IL-14.

Brief Summary Text (95):
Attachment of the targeting ligand to the porous particle either directly or with a covalent or non-covalent tether should provide a site-directed ultrasound contrast agent whose selectivity is related to the binding coefficient and specificity of the ligand. One method of attaching a targeting ligand is to incorporate a silane bonded to a silica surface on the particle (for general principles, see "The preparation of immobilized proteins covalently coupled through silane coupling agents to inorganic supports," by H. H. Weetall, Adv. Mol. Cell Biol., 15A (1996) pp. 161-192). If the particle itself is silica, the desired silane can be directly reacted with the particle to modify the surface.

Brief Summary Text (99):
If the particle is not completely silica, another method would be to incorporate silanols (Si--OH groups) on or within the particle being prepared. This could be accomplished by preparing the major part of the particle in the presence of silica sol (small silica particles), which would then be physically incorporated within the matrix of the main substance (e.g., calcium phosphate particles). For example, one could prepare calcium carbonate particles with small amount (0.5-10%) of small silica sol (from 5 to 1000 nm) during the preparation. Some of these sol particles would be incorporated and provide the necessary Si--OH groups onto which subsequent silane reactions could be done.

Brief Summary Text (102):
The porous inorganic targeted particles of the present invention are administered with an acceptable carrier to a person to enhance the contrast and resolution of ultrasound imaging of the tissue or organ system that is being targeted and imaged. Thus, the inorganic particles must have acceptable biocompatibility and toxicity properties in humans. The biocompatibility criteria will depend in part on the type of ultrasound imaging application and route of administration of the ultrasound contrast agent. For example, the biocompatibility criteria may be different for gastrointestinal administration than for parenteral administration of the contrast agent.

Brief Summary Text (104):
The porous inorganic particles of the invention may be coated with an organic material, such as those materials described below, to control the stability, pharmacokinetics, targeting, and biological effects of the particles in vivo. Such coating is preferably done before attachment of the targeting ligand, but in some cases may be done afterwards. Coating or microencapsulation of the particles can be used to enhance their stability in the formulation, to prevent aggregation, to alter

their tissue distribution in the body and their elimination from the body, to reduce toxicity or enhance effectiveness, to reduce the adherence of biological materials which trigger immune reactions or thromboembolic reactions, to control the dissolution rate of soluble particles, and to control the permeation of water and other substances into and out of the particle matrix, among other uses.

Detailed Description Text (6):
The resultant hollow silica particles are then heated in a temperature controlled furnace at a temperature and for a time that will produce condensed forms of silica. The temperature and duration of the heating of the porous partilces is selected such that the particles obtained have the desired solubility in aqueous solution.

Detailed Description Text (14):
The resultant hollow silica particles are then heated in a temperature controlled furnace at a temperature and for a time that will produce condensed forms of silica. The temperature and duration of the heating of the porous partilces is selected such that the particles obtained have the desired solubility in aqueous solution.

CLAIMS:

P is a porous particle of an inorganic material having an average particle diameter of about 0.05 to 500 microns and containing an entrapped gas or liquid;

10. A contrast agent according to claim 1, wherein the porous particles have a single pore which is entirely or partially enclosed by a shell of the inorganic material.

12. A contrast agent according to claim 1, wherein the porous particles have a plurality of pores which are entirely or partially enclosed by the inorganic material.

13. A contrast agent according to claim 1, wherein the porous particles of inorganic material have a density of less than about 90% of the density of the inorganic material in a solid non-porous state.

14. A contrast agent according to claim 13, wherein the porous particles of inorganic material have a density of less than about 60% of the density of the inorganic material in a solid non-porous state.

15. A contrast agent according to claim 14, wherein the porous particles of inorganic material have a density of 0.2% to 50% of the density of the inorganic material in a solid non-porous state.

16. A contrast agent according to claim 1, wherein the porous particles of inorganic material are substantially spherical in shape.

18. A contrast agent according to claim 17, wherein the porous particles of inorganic material are coated with an organic material.

L7: Entry 10 of 62 File: USPT

DOCUMENT-IDENTIFIER: US 6358532 B2
TITLE: Calcium phosphate microcarriers and microspheres

Brief Summary Text (4):
Revolutionary advances in biotechnology and genetic engineering have created enormous potential for marketing cellular by-products, including for example, proteins, including protein pharmaceuticals such as interferon, monoclonal antibodies, TPA (Tissue Plasminogen Activator), growth factors, insulin, and cells for transplantation. The demand for these products has grown tremendously and will continue to do so, creating a need for efficient methods of producing industrial quantities of cell-derived pharmaceuticals and other products. Further, the demand for efficient methods of analyzing and isolating biological products through chromatographic technology, and the need to improve bio-implantables continues to grow.

Brief Summary Text (12):
An example of the use of non-suspendable or porous ceramic particles for cell culture is taught by U.S. Pat. No. 5,262,320 (G. Stephanopoulos) which describes a packed bed of ceramic particles around and through which oxygen and growth media are circulated to encourage growth of cells. U.S. Pat. No. 4,987,068 (W. Trosch et al.) also teaches the use of porous inorganic (glass) spheres in fixed bed or fluidized bed bioreactors. The pores of the particles act as sites for the culture of cells. Conversely, Richard Peindhl, in U.S. Pat. No. 5,538,887, describes a smooth surface cell culture apparatus which would limit cell attachment to chemical adhesion and prevent mechanical interlocking.

Detailed Description Text (22):
CaP non-suspendable microcarrier spheres with open porosity are prepared as described above using a conventional spray drying method or pelletizing method well known in the art from either a modified sol gel process or powder slurry process. Also the method taught by Martin (U.S. Pat. No. 3,875,273, supra.) can be used to form open porous microcarriers. The preferred shape of the individual microcarrier produced by the methods described above is sphere-like with a continuous porous phase (FIGS. 1, 1.8). An alternative shape of microcarrier is a hollow microsphere having a continuous porous wall that connects the central microsphere void to the outer surface (FIGS. 1, 1.2). This form of microcarrier can be produced by the reactor nozzle method taught by Torobin (U.S. Pat. No. 5,397,759). The open porosity of microspheres is created by sintering at a lower temperature of about 1100.degree. C., which is less than that typically required to densify the material, or by adding a pore former as previously discussed, followed by sintering. The preferred embodiment of this invention requires microspheres with densities greater than 1.12 gm/cc for packed or fluidized bed bioreactors.

Detailed Description Text (25):
The processing methods as set forth for CaP microsphere fabrication (e.g., CaP Microbead Processing Method for Producing a Suspendable Microcarrier Substrate and Alternate Method for Fabricating Hollow CaP Microcarriers with Diameters Less Than 500 Micrometers (Sol Gel Type System) described above) can be used to produce microspheres for use in chromatographic applications. In this application, a preferred embodiment for the microspheres is in the size range of about 10 to 100 micrometers diameter with open porosity in the range of about 20% to about 60% and a pore size range from about 0.01 to about 0.5 micrometers. Microsphere sizes larger

than 100 micrometers, up to about 2 millimeters diameter in either the hollow or non-hollow sphere form, improve permeability by minimizing the resistance to flow in the chromatographic column while maintaining the ability to separate and purify proteins, enzymes, nucleic acids, viruses, and other macromolecules. In addition, the thin wall of the hollow porous microsphere improves permeability for greater efficiency of separation and purification..

Detailed Description Text (33):
An object of this invention is to provide appropriate forms of calcium phosphate ceramic materials to be fabricated in specific shapes and sizes for anchorage-dependent mammalian cell culturing applications. Fabricated forms of the calcium phosphate ceramic to be used as microcarriers in, for example, mammalian cell culture applications include hollow microspheres, solid spheres, aggregates of microspheres, multi-pore aggregates, polymeric and glass CaP composites. A variety of coatings that can be made highly porous or combined with organic or polymeric materials, including growth factors, to form composite structures also can be used in conjunction with these fabricated forms. Combinations of the aforementioned fabricated forms also can be used to make the microcarriers of the present invention. To achieve the objects of this invention, appropriate mixtures of hydroxylapatite, tricalcium phosphate, and/or other CaP compounds and, in certain cases, an open pore phase are used to enhance cellular growth through the higher surface area of the porous structure. Closed porosity is used to maintain buoyancy in growth media. Although more limited in application, calcium carbonate can be used in granular form, as a coating on a substrate carrier for cell culturing applications or as the Ca phase in polymeric composites. A major advantage of the CaP ceramic microcarriers is that the finished material can be heated to as high as 1,000.degree. C. for decomposing organic cell culture components to recycle the microcarrier after its use in culture. This heating step can not be done with the polymeric/CaP composite microcarriers described herein. Other advantages of the CaP substrate as a microcarrier for cell culturing applications, as compared to polymeric materials, are that the CaP substrate is dimensionally stable, due to non-swelling, by absorption of media.

Detailed Description Text (35):
U.S. Pat. No. 5,397,759 by Leonard Torobin teaches a process for fabricating porous ceramic hollow microspheres of uniform diameter and uniform wall thickness in sizes ranging from 1-4 mm in diameter. U.S. Pat. No. 5,225,123 by Leonard Torobin also teaches a process for fabricating hollow ceramic microspheres with closed porosity. The present invention uses aspects of this technology to produce a suspendable calcium phosphate ceramic for use in cell culture applications. An alternative technology for fabricating porous ceramic hollow spheres is described in U.S. Pat. No. 3,875,273 by Robert M. Martin. There also are other processes for fabricating hollow microspheres from ceramic materials as described by David Wilcox in Hollow and Solid Spheres and Microspheres: Science and Technology Associated With Their Fabrication and Application, Materials Research Society Symposium Proceedings, Volume 372, 1995. These fabrication methods include sacrificial cores, nozzle-reactor systems, emulsion/phase separation techniques (including sol gel processing), and mechanical attrition. Although these approaches do not specifically address calcium phosphate materials or cell culture microcarrier system applications, the described processes could be modified to produce the media suspendable calcium phosphate microcarrier systems of the present invention based on teachings herein. However, the aforementioned technologies must be combined with either commercial sources of calcium phosphate materials or be allied to the chemical formulation of hydroxylapatite and/or other calcium phosphate compoundssuch as tricalcium phosphate (tribasic calcium phosphate) in order to produce the carriers of the present invention. These materials are of primary interest, since they can be fabricated in dense non-permeable forms as taught by A. Tampieri in the Journal of Material Science: Materials in Medicine, Vol. 8, pp. 29-37, 1997.

Detailed Description Text (48):
An alternative method for fabricating ceramic hollow spheres is set forth in U.S. Pat. No. 3,875,273 by Martin and can be used to manufacture the CaP microspheres of the present invention. However, it is not as readily scaled for high volume production needs. The Martin method produces porous ceramic microbeads which subsequently require sealing of the outer microsphere surface with a polymeric film

to attain a suspendable microcarrier.

Detailed Description Text (128):
14. Leonard B. Torobin, U.S. Pat. No. 5, 397,759, Hollow Porous Microspheres Made From Dispersed Particle Compositions, Mar. 14, 1995.

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L5: Entry 14 of 14 File: USPT

DOCUMENT-IDENTIFIER: US 3921636 A
TITLE: Novel drug delivery device

Detailed Description Text (9):
While the above FIGS. 1 through 8 inclusive are illustrative of various drug delivery devices that can be made according to the invention, it is to be understood that the illustrated devices are not to be construed as limiting, as the drug delivery device of the invention can take shapes, sizes and forms for administering drug to different areas of the body. For example, the invention includes external and internal drug delivery devices such as skin patches, sublingual drug delivery devices, peroral devices, arterial devices, nasal and ear drug delivery devices, ocular inserts, suture materials, plastic heart valves, hip joints, bone pins, pessaries, prosthesis, artificial glands, cervical rings, troches, or intrauterine drug delivery devices of any shape. In each instance, the drug delivery device has a matrix containing a plurality of reservoirs containing drug. Both the matrix and the reservoir are permeable to the passage of drug by diffusion, and/or microporous flow with rate of permeation from the reservoir being lower than the rate of permeation through the matrix.

Detailed Description Text (25):
To provide the microcapsule reservoirs, particles or solutions of drugs can be encapsulated with thin coatings of the encapsulating material to form microcapsules having an interior chamber containing the drug. Alternatively, the encapsulating material can be uniformly impregnated with the drug or drug solution, or a mixture of drugs, to form microcapsules which are a matrix having the drug distributed therethrough. If desired, particles of a known drug carrier, such as starch, gum acacia, charcoal, gum tragacanth, calcium carbonate, poly(vinylchloride), and the like, can be impregnated with the drug and encapsulated with another material such as the encapsulating materials previously discussed. These latter materials then function as the membrane which meters the flow of drug to the matrix.

Detailed Description Text (44):
In the specification and the accompanying claims, the term "drug" broadly includes, without limitation, physiologically or pharmacologically active substances for producing a localized or systemic effect or effects in animals, especially mammals. The active drugs that can be administered by the drug delivery device of the invention include, without limitation: for example, drugs acting on the central nervous system such as, hypnotics and sedatives such as pentobarbital sodium, phenobarbital, secobarbital, thiopental, etc.; heterocyclic hypnotics such as dioxopiperidines, and glutarimides; hypnotics and sedatives such as amides and ureas exemplified by diethylisovaleramide and .alpha.-bromoisovaleryl urea and the like; hypnotics and sedative alcohols such as carbomal, naphthoxyethanol, methylparaphenol and the like; and hypnotic and sedative urethans, disulfanes and the like; psychic energizers such as isocarboxacid, nialamide, phenelzine, imipramine, tranylcypromine, pargylene and the like; tranquilizers such as chloropromazine, promazine, fluphenazine reserpine, deserpidine, meprobamate, benzodiazepines such as chlordiazepoxide and the like; anticonvulsants such as primidone, diphenylhydantoin, ethotoin, pheneturide, ethosuximide and the like; muscle relaxants and antiparkinson agents such as mephenesin, methocarbomal, trihexylphenidyl, biperiden, levo-dopa, also known as L-dopa and 1-.beta.-3-4-dihydroxyphenylalanine, and the like; analgesics such as morphine, codeine, meperidine, nalorphine and the like;

anti-pyretics and anti-inflammatory agents such as aspirin, salicylamide, sodium salicylamide and the like; local anesthetics such as procaine, lidocaine, naepaine, piperocaine, tetracaine, dibucaine and the like; antispasmodics and antiulcer agents such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine, prostaglandins such as PGE.sub.1, PGE.sub.2, PGF.sub.1.sub..alpha., PGF.sub.2.sub..alpha., PGA and the like; antimicrobials such as penicillin, tetracycline, oxytetracycline, chlorotetracycline, chloramphenicol, sulfonamides and the Like; anti-malarials such as 4-aminoquinolines, 8-aminoquinolines and pyrimethamine; hormonal agents such as prednisolone, cortisone, cortisol and triamcinoline; androgenic steroids, for example, methyltestosterone, fluoximesterone and the like; estrogenic steroids, for example, 17.beta.-estradiol and ethinyl estradiol; progestational steriods, for example 17.alpha.-hydroxyprogesterone acetate, 19-nor-progesterone, norethindrone and the like; sympathomimetic drugs such as epinephrine, amphetamine, ephedrine, norepinephrine and the like; cardiovascular drugs, for example, procainamide, amyl nitrate, nitroglycerin, dipyridamole, sodium nitrate, mannitol nitrate and the like; diuretics, for example, chlorothiazide, flumethiazide and the like; antiparasitic agents such as bephenium hydroxynaphthoate and dichlorophen, dapsone and the like; neoplastic agents such as mechlorethamine, uracil mustard, 5-fluorouracil, 6-thioquanine, procarbazine and the like; hypoglycemic drugs such as insulins, protamine zinc insulin suspension, and other art known extended insulin suspension, sulfonylureas such as tolbutamide, acetohexamide, tolazamide, and chlorpropamide, the biguanides and the like; nutritional agents such as vitamins, essential amino acids, essential fats and the like; and other physiologically or pharmacologically active agents. Also the drugs can be present as the pharmacologically acceptable derivatives, such as ethers, esters, amides, acetals, etc. that lend themselves to passage into the circulatory system. For highly water soluble drugs, it is preferable that the matrix or the reservoir, or both be formed from a material that is substantially impermeable to water to essentially prevent dilution of the drug by absorption of body fluids into the devices with an accompanying decrease in drug release rate. These derivatives can be prepared by art known techniques and then used in the practice of the invention. Of course, the drug derivative should be such as to convert to the active drug within the body through the action of body enzymes assisted transformations, pH, specific organ activities, and the like.

Detailed Description Text (51):
A nasal anti-allergenic drug delivery device is prepared by first mixing with 10 g of dry corn starch having a particle size of from 5 to 7 millimicrons, 5 ml. of a rag weed pollen liquid extract containing biologically active microsolutes of the pollen. The mixing is continued in a bench V-blender until all the pollen liquid extract is absorbed by the starch. Next, a portion of the starch particles saturated with the liquid are suspended in a column of dry air in a Wurster fluidized bed coating apparatus and spray coated with a solution of regenerated, leached cellulose xanthate and then maintained in a fluidizing flow of dry air until the cellulose xanthate coating is dry. Next, the air flow is cut off and the coated starch particles fall to the bottom of the apparatus for collection.

Detailed Description Text (52):
The recovered particles are tiny drug reservoirs having biologically active material and a starch carrier surrounded and enclosed by a cellulose xanthate wall. This wall contains pores of about 24A diameter. A portion of these particles are placed in simulated nasal gluids and the rate of release of active material is measured and compared with the rate of release of active material from the starch particles which were not coated. The cellulose xanthate coated particles release active material at a slower substantially constant controlled rate (0 order time dependence). Thus, the cellulose xanthate coating functions as an active agent release rate controlling wall. A portion of the coated particles are dispersed through and trapped in a matrix of fine nylon fibers.

Detailed Description Text (65):
A drug delivery device for the controlled, oral administration of water-soluble prednisolone is prepared as follows: first, a plurality of drug reservoirs comprising porous, discrete particles of polymerized poly(vinyl chloride) of about 100 microns diameter are prepared by mixing 100 g of suspension grade poly(vinyl chloride) resin wiith 50 g of octyl diphenyl phosphate and 10 g of prednisolone disodium phosphate at

room temperature into a sticky, wet mass. Next, the temperature of the mixture is raised to 80.degree.C for about 3 to 7 minutes, while stirring, to form dry, free flowing, discrete drug reservoirs. The reservoirs are uniformly dispersed through a matrix by mixing 50 g of reservoirs containing the prednisolone with 140 g of polydimethylsiloxane, 10 g of silicone oil, and 0.5 g of stannous octoate. After mixing the ingredients, the mixture is charged into pill molds and allowed to cure for 30 minutes. Oral administration of the resulting device yields a controlled essentially constant rate of release of prednisolone phosphate to the gastrointestinal tract to give a more uniform blood level of prednisolone over a longer period of time than is achieved when prednisolone alcohol is administered by standard prior art pills.

Detailed Description Text (67):
Following the procedure of Example 6, a plurality of porous drug reservoirs comprised of commercially available, prepolymerized particles of poly(vinyl chloride) having prednisolone distributed therethrough is prepared by mixing 100 milligrams of prednisolone disodium phosphate, 1930 milligrams of poly(vinyl chloride) particles, 260 milligrams of standard grade starch binder, 50 milligrams of lubricant sodium benzoate and 200 milligrams of sodium caprylate solubilizing agent. The mixing is continued until a homogenous mixture is formed. Next, the mixture is pressed and then sieved through a No. 200 sieve to give reservoirs of about 75 microns containing the drug. The reservoirs are then distributed in a matrix as in Example 6 to provide a drug delivery device.

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Search Results - Record(s) 1 through 14 of 14 returned.

☐ 1. Document ID: US 6416740 B1

L5: Entry 1 of 14 File: USPT

US-PAT-NO: 6416740
DOCUMENT-IDENTIFIER: US 6416740 B1

TITLE: Acoustically active drug delivery systems

DATE-ISSUED: July 9, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.5, 424/9.51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 6403056 B1

L5: Entry 2 of 14 File: USPT

US-PAT-NO: 6403056
DOCUMENT-IDENTIFIER: US 6403056 B1

TITLE: Method for delivering bioactive agents using cochleates

DATE-ISSUED: June 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.51; 424/400, 424/450, 424/502, 424/9.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 3. Document ID: US 6309669 B1

L5: Entry 3 of 14 File: USPT

US-PAT-NO: 6309669

DOCUMENT-IDENTIFIER: US 6309669 B1

TITLE: Therapeutic treatment and prevention of infections with a bioactive materials encapsulated within a biodegradable-biocompatible polymeric matrix

DATE-ISSUED: October 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Setterstrom; Jean A.	Alpharetta	GA		
Van Hamont; John E.	Fort Meade	MD		
Reid; Robert H.	McComas	CT		
Jacob; Elliot	Silver Spring	MD		
Jeyanthi; Ramasubbu	Columbia	MD		
Boedeker; Edgar C.	Chevy Chase	MD		
McQueen; Charles E.	Olney	MD		
Jarboe; Daniel L.	Silver Spring	MD		
Cassels; Frederick	Ellicott City	MD		
Brown; William	Denver	CO		
Thies; Curt	Ballwin	MO		
Tice; Thomas R.	Birmington	AL		
Roberts; F. Donald	Dover	MA		
Friden; Phil	Beford	MA		

US-CL-CURRENT: 424/486; 424/422, 424/423, 424/424, 424/425, 424/484

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 4. Document ID: US 6123923 A

L5: Entry 4 of 14 File: USPT

US-PAT-NO: 6123923
DOCUMENT-IDENTIFIER: US 6123923 A

TITLE: Optoacoustic contrast agents and methods for their use

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Wu; Yunqiu	Tucson	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.1, 424/9.2, 424/9.3, 424/9.6, 514/410

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 5. Document ID: US 6120751 A

L5: Entry 5 of 14 File: USPT

US-PAT-NO: 6120751
DOCUMENT-IDENTIFIER: US 6120751 A

TITLE: Charged lipids and uses for the same

DATE-ISSUED: September 19, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.51; 264/4, 264/4.1, 424/450, 424/502, 424/9.52, 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC | Draw Desc | Image

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☐ 6. Document ID: US 6090800 A

L5: Entry 6 of 14 File: USPT

US-PAT-NO: 6090800
DOCUMENT-IDENTIFIER: US 6090800 A

TITLE: Lipid soluble steroid prodrugs

DATE-ISSUED: July 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Shen; DeKang	Tucson	AZ		

US-CL-CURRENT: 514/180; 552/574

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC | Draw Desc | Image

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☐ 7. Document ID: US 6028066 A

L5: Entry 7 of 14 File: USPT

US-PAT-NO: 6028066
DOCUMENT-IDENTIFIER: US 6028066 A

TITLE: Prodrugs comprising fluorinated amphiphiles

DATE-ISSUED: February 22, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 514/180; 514/169, 552/507

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC
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☐ 8. Document ID: US 5861387 A

L5: Entry 8 of 14 File: USPT

US-PAT-NO: 5861387
DOCUMENT-IDENTIFIER: US 5861387 A

TITLE: Controlled release systems and low dose androgens

DATE-ISSUED: January 19, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Labrie; Fernand	Quebec			CA
Lepage; Martin	Quebec			CA

US-CL-CURRENT: 514/169; 424/457, 424/478, 514/170, 514/177, 514/179, 514/964, 514/965

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC
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☐ 9. Document ID: US 5814340 A

L5: Entry 9 of 14 File: USPT

US-PAT-NO: 5814340
DOCUMENT-IDENTIFIER: US 5814340 A

TITLE: Controlled release systems and low dose androgens

DATE-ISSUED: September 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Labrie; Fernand	Quebec			CA
Lepage; Martin	Quebec			CA

US-CL-CURRENT: 424/489; 424/493, 424/497, 428/402, 514/169, 514/170, 514/177, 514/179, 514/964, 523/113

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC
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☐ 10. Document ID: US 5629303 A

L5: Entry 10 of 14 File: USPT

US-PAT-NO: 5629303
DOCUMENT-IDENTIFIER: US 5629303 A

TITLE: Controlled release systems and low dose androgens

DATE-ISSUED: May 13, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Labrie; Fernand	Quebec			CA
Lepage; Martin	Quebec			CA

US-CL-CURRENT: 514/169; 514/170, 514/177, 514/179

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 11. Document ID: US 5541172 A

L5: Entry 11 of 14 File: USPT

US-PAT-NO: 5541172
DOCUMENT-IDENTIFIER: US 5541172 A

TITLE: Controlled release systems and low dose androgens

DATE-ISSUED: July 30, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Labrie; Fernand	Quebec			CA
Lepage; Martin	Quebec			CA

US-CL-CURRENT: 514/169; 424/422, 514/170, 514/177, 514/179, 514/964, 514/965, 523/113

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 12. Document ID: US 5534269 A

L5: Entry 12 of 14 File: USPT

US-PAT-NO: 5534269
DOCUMENT-IDENTIFIER: US 5534269 A

TITLE: Method of producing sustained-release preparation

DATE-ISSUED: July 9, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Igari; Yasutaka	Kobe			JP
Yamamoto; Kazumichi	Nara			JP
Okamoto; Kayoko	Osaka			JP
Yamagata; Yutaka	Kobe			JP

US-CL-CURRENT: 424/489; 424/484, 424/85.4, 514/2, 514/21, 514/964

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 13. Document ID: US 5434146 A

L5: Entry 13 of 14 File: USPT

US-PAT-NO: 5434146
DOCUMENT-IDENTIFIER: US 5434146 A

TITLE: Controlled release systems and low dose androgens

DATE-ISSUED: July 18, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Labrie; Fernand	Quebec			CA
Lepage; Martin	Quebec			CA

US-CL-CURRENT: 514/169; 424/422, 514/170, 514/177, 514/179, 523/113

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 14. Document ID: US 3921636 A

L5: Entry 14 of 14 File: USPT

US-PAT-NO: 3921636
DOCUMENT-IDENTIFIER: US 3921636 A

TITLE: Novel drug delivery device

DATE-ISSUED: November 25, 1975

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zaffaroni; Alejandro	Atherton	CA		

US-CL-CURRENT: 424/432; 128/833, 424/424, 424/425, 424/431, 424/433, 424/436, 424/468, 424/486

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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L10: Entry 1 of 11 File: USPT

DOCUMENT-IDENTIFIER: US 6416740 B1
TITLE: Acoustically active drug delivery systems

Detailed Description Text (23):
"Clathrate" refers to a solid, semi-porous or porous particle which may be associated with vesicles. In a preferred form, the clathrates may form a cage-like structure containing cavities which comprise one or more vesicles bound to the clathrate, if desired. A stabilizing material may, if desired, be associated with the clathrate to promote the association of the vesicle with the clathrate. Clathrates may be formulated from, for example, porous apatites, such as calcium hydroxyapatite, and precipitates of polymers and metal ions, such as alginic acid precipitated with calcium salts.

Detailed Description Text (154):
Gaseous precursors derived from salts are preferably selected from the group consisting of alkali metal salts, ammonium salts and mixtures thereof. More preferably, the salt is selected from the group consisting of carbonate, bicarbonate, sesquecarbonate, aminomalonate and mixtures thereof. Examples of suitable gaseous precursor materials which are derived from salts include, for example, lithium carbonate, sodium carbonate, potassium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, magnesium carbonate, calcium carbonate, magnesium bicarbonate, ammonium carbonate, ammonium bicarbonate, ammonium sesquecarbonate, sodium sesquecarbonate, sodium aminomalonate and ammonium aminomalonate. Aminomalonate is well known in the art, and its preparation is described, for example, in Thanassi, Biochemistry, 9(3):525-532 (1970); Fitzpatrick et al., Inorganic Chemistry, 13(3):568-574 (1974); and Stelmashok et al., Koordinatsionnaya Khimiya, 3(4):524-527 (1977), the disclosures of which are hereby incorporated herein by reference in their entirety.

Detailed Description Text (286):
The compositions of the invention, including the steroid prodrugs, may be administered to the patient by a variety of different means. The means of administration will vary depending upon the intended application. As one skilled in the art would recognize, administration of the steroid prodrug or the steroid prodrug in combination with the stabilizing materials and/or vesicles of the present invention can be carried out in various fashions, for example, topically, including ophthalmic, dermal, ocular and rectal, intrarectally, transdermally, orally, intraperitoneally, parenterally, intravenously, intralymphatically, intratumorly, intramuscularly, interstitially, intraarterially, subcutaneously, intraocularly, intrasynovially, transepithelially, pulmonarily via inhalation, ophthalmically, sublingually, buccally, or via nasal inhalation via insufflation, nebulization, such as by delivery of an aerosol. Preferably, the steroid prodrugs and/or stabilizing materials of the present invention are administered intravenously or topically/transdermally. In the case of inhalation, a gaseous precursor delivered with a composition of the present invention such that the gaseous precursor is in liquid, gas, or liquid and gas form.

Other Reference Publication (13):
Luo, P. et al., "Preparing hydroxyapatite powders with controlled morphology", Biomaterials, 1996, 17(20), 1959-1964.

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☐ 1. Document ID: US 6416740 B1

L10: Entry 1 of 11 File: USPT

US-PAT-NO: 6416740
DOCUMENT-IDENTIFIER: US 6416740 B1

TITLE: Acoustically active drug delivery systems

DATE-ISSUED: July 9, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.5, 424/9.51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6403056 B1

L10: Entry 2 of 11 File: USPT

US-PAT-NO: 6403056
DOCUMENT-IDENTIFIER: US 6403056 B1

TITLE: Method for delivering bioactive agents using cochleates

DATE-ISSUED: June 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.51; 424/400, 424/450, 424/502, 424/9.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6231834 B1

L10: Entry 3 of 11 File: USPT

US-PAT-NO: 6231834
DOCUMENT-IDENTIFIER: US 6231834 B1

TITLE: Methods for ultrasound imaging involving the use of a contrast agent and multiple images and processing of same

DATE-ISSUED: May 15, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Fritz; Thomas A.	Tucson	AZ		
Gertz; Edward W.	Paradise Valley	AZ		

US-CL-CURRENT: 424/9.51; 424/9.52, 600/431

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6139819 A

L10: Entry 4 of 11 File: USPT

US-PAT-NO: 6139819
DOCUMENT-IDENTIFIER: US 6139819 A

TITLE: Targeted contrast agents for diagnostic and therapeutic use

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Fritz; Thomas A.	Tucson	AZ		
Gertz; Edward W.	Paradise Valley	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6123923 A

L10: Entry 5 of 11 File: USPT

US-PAT-NO: 6123923
DOCUMENT-IDENTIFIER: US 6123923 A

TITLE: Optoacoustic contrast agents and methods for their use

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Wu; Yunqiu	Tucson	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.1, 424/9.2, 424/9.3, 424/9.6, 514/410

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 6. Document ID: US 6120751 A

L10: Entry 6 of 11 File: USPT

US-PAT-NO: 6120751
DOCUMENT-IDENTIFIER: US 6120751 A

TITLE: Charged lipids and uses for the same

DATE-ISSUED: September 19, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.51; 264/4, 264/4.1, 424/450, 424/502, 424/9.52, 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 7. Document ID: US 6090800 A

L10: Entry 7 of 11 File: USPT

US-PAT-NO: 6090800
DOCUMENT-IDENTIFIER: US 6090800 A

TITLE: Lipid soluble steroid prodrugs

DATE-ISSUED: July 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Shen; DeKang	Tucson	AZ		

US-CL-CURRENT: 514/180; 552/574

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 8. Document ID: US 6071494 A

L10: Entry 8 of 11 File: USPT

US-PAT-NO: 6071494
DOCUMENT-IDENTIFIER: US 6071494 A

TITLE: Methods for diagnostic imaging using a contrast agent and a renal vasodilator

DATE-ISSUED: June 6, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.4; 424/9.3, 424/9.51, 424/9.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 9. Document ID: US 6033645 A

L10: Entry 9 of 11 File: USPT

US-PAT-NO: 6033645
DOCUMENT-IDENTIFIER: US 6033645 A

TITLE: Methods for diagnostic imaging by regulating the administration rate of a contrast agent

DATE-ISSUED: March 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ	85749	
Matsunaga; Terry	Tucson	AZ	85710	
Fritz; Thomas A.	Tucson	AZ	85711	
Ramaswami; Varadarajan	Tucson	AZ	85715	

US-CL-CURRENT: 424/9.5; 424/450, 424/9.51, 424/9.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 10. Document ID: US 6028066 A

L10: Entry 10 of 11 File: USPT

US-PAT-NO: 6028066
DOCUMENT-IDENTIFIER: US 6028066 A

TITLE: Prodrugs comprising fluorinated amphiphiles

DATE-ISSUED: February 22, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 514/180; 514/169, 552/507

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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L10: Entry 6 of 11 File: USPT

DOCUMENT-IDENTIFIER: US 6120751 A
TITLE: Charged lipids and uses for the same

Detailed Description Text (11):
"Clathrate" refers to a solid, semi-porous or porous particle which may be associated with vesicles. Preferably, clathrates form a cage-like structure containing cavities which comprise one or more vesicles bound to the clathrate. A stabilizing material may be associated with the clathrate to promote the association of the vesicle with the clathrate. Clathrates may be formulated from, for example, porous apatites, such as calcium hydroxyapatite, and precipitates of polymers and metal ions, such as alginic acid precipitated with calcium salts.

Detailed Description Text (147):
Polymers useful to stabilize the vesicles of the present invention may be of natural, semi-synthetic (modified natural) or synthetic origin. Suitable natural polymers include naturally occurring polysaccharides, such as, for example, arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans (such as, for example, inulin), levan, fucoidan, carrageenan, galatocarolose, pectic acid, pectins, including amylose, pullulan, glycogen, amylopectin, cellulose, dextran, dextrin, dextrose, glucose, polyglucose, polydextrose, pustulan, chitin, agarose, keratin, chondroitin, dermatan, hyaluronic acid, alginic acid, xanthin gum, starch and various other natural homopolyner or heteropolymers, such as those containing one or more of the following aldoses, ketoses, acids or amines: erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, dextrose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, mannitol, sorbitol, lactose, sucrose, trehalose, maltose, cellobiose, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine, and neuraminic acid, and naturally occurring derivatives thereof Accordingly, suitable polymers include, for example, proteins, such as albumin, polyalginates, and polylactide-coglycolide polymers. Exemplary semi-synthetic polymers include carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and methoxycellulose. Exemplary synthetic polymers include polyphosphazenes, hydroxyapatites, fluoroapatite polymers, polyethylenes (such as, for example, polyethylene glycol (including for example, the class of compounds referred to as Pluronics.RTM., commercially available from BASF, Parsippany, N.J.), polyoxyethylene, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes (such as, for example, polyvinyl alcohol (.PVA), polyvinyl chloride and polyvinylpyrrolidone), polyamides including nylon, polystyrene, polylactic acids, fluorinated hydrocarbon polymers, fluorinated carbon polymers (such as, for example, polytetrafluoroethylene), acrylate, methacrylate, and polymethylmethacrylate, and derivatives thereof. Methods for the preparation of vesicles which employ polymers to stabilize vesicle compositions will be readily apparent to one skilled in the art, in view of the present disclosure, when coupled with information known in the art, such as that described and referred to in Unger, U.S. Pat. No. 5,205,290, the disclosure of which is hereby incorporated by reference herein in its entirety.

Detailed Description Text (163):

Gaseous precursors derived from salts are preferably selected from the group consisting of alkali metal salts, ammonium salts and mixtures thereof More preferably, the salt is selected from the group consisting of carbonate, bicarbonate, sesquecarbonate, aminomalonate and mixtures thereof Suitable gaseous precursor materials which are derived from salts include, for example, lithium carbonate, sodium carbonate, potassium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, magnesium carbonate, calcium carbonate, magnesium bicarbonate, ammonium carbonate, ammonium bicarbonate, ammonium sesquecarbonate, sodium sesquecarbonate, sodium aminomalonate and ammonium aminomalonate. Aminomalonate is well known in the art, and its preparation is described, for example, in Thanassi, Biochemistry, 9(3):525-532 (1970); Fitzpatrick et al., Inorganic Chemistry, 13(3):568-574 (1974); and Stelmashok et al., Koordinatsionnaya Khimiya, 3(4):524-527 (1977). The disclosures of each of these publications are hereby incorporated herein by reference in their entirety.

Detailed Description Text (321):
The compositions of the invention may be administered to the patient by a variety of different means, which will vary depending upon the intended application. As one skilled in the art would recognize, administration of the compositions of the present invention can be carried out in various fashions including, for example, topically, including ophthalmic, dermal, ocular and rectal, intrarectally, transdermally, orally, intraperitoneally, parenterally, intravenously, intralymphatically, intratumorly, intramuscularly, interstitially, intra-arterially, subcutaneously, intraocularly, intrasynovially, transepithelially, transdermally, pulmonarily via inhalation, ophthalmically, sublingually, buccally, or nasal inhalation via insufflation or nebulization.

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L7: Entry 32 of 62 File: USPT

DOCUMENT-IDENTIFIER: US 5948438 A
TITLE: Pharmaceutical formulations having improved disintegration and/or absorptivity

Brief Summary Text (23):
In U.S. Pat. No. 4,744,987 (Mehra, et al.), a particulate co-processed microcrystalline cellulose and calcium carbonate composition is described wherein the respective components are present in a weight ratio of 75:25 to 35:65. The co-processed composition is said to be prepared by forming a well-dispersed aqueous slurry of microcrystalline cellulose and calcium carbonate and then drying the slurry to yield a particulate product. The combination of these two ingredients is said to provide a lower cost excipient which has tableting characteristics similar to those of microcrystalline cellulose and which would satisfy a need for an economical excipient with good performance that is desired by the vitamin market.

Brief Summary Text (48):
Microcrystalline cellulose is a well-known tablet diluent, binder and disintegrant. Its chief advantage over other excipients is that it can be directly compressed into self-binding tablets which disintegrate rapidly when placed into water. This widely-used ingredient is prepared by partially depolymerizing cellulose obtained as a pulp from fibrous plant material with dilute mineral acid solutions. Following hydrolysis, the hydrocellulose thereby obtained is purified via filtration and an aqueous slurry is spray dried to form dry, white odorless, tasteless crystalline powder of porous particles of various sizes. Another method of preparing microcrystalline cellulose is disclosed in U.S. Pat. No. 3,141,875. This reference discloses subjecting cellulose to the hydrolytic action of hydrochloric acid at boiling temperatures so that amorphous cellulosic material can be removed and aggregates of crystalline cellulose are formed. The aggregates are collected by filtration, washed with water and aqueous ammonia and disintegrated into small fragments, often called cellulose crystallites by vigorous mechanical means such as a blender. Microcrystalline cellulose is commercially available in several grades which range in average particle size from 20 to 200 microns.

Brief Summary Text (104):
In addition to one or more active ingredients, additional pharmaceutically acceptable excipients (in the case of pharmaceuticals) or other additives known to those skilled in the art (for non-pharmaceutical applications) can be added to the novel excipient prior to preparation of the final product. For example, if desired, any generally accepted soluble or insoluble inert pharmaceutical filler (diluent) material can be included in the final product (e.g., a solid dosage form). Preferably, the inert pharmaceutical filler comprises a monosaccharide, a disaccharide, a polyhydric alcohol, inorganic phosphates, sulfates or carbonates, and/or mixtures thereof. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, xylitol, fructose, sorbitol, calcium phosphate, calcium sulfate, calcium carbonate, "off-the-shelf" microcrystalline cellulose, mixtures thereof, and the like.

Brief Summary Text (108):
A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g. pharmaceutical agents) which may be used in the compositions of the present invention include both water soluble and water insoluble drugs. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine,

dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), anti-tussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g., clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psycho-tropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

Brief Summary Text (110):
The locally active agent(s) include antifungal agents (e.g., amphotericin B, clotrimazole, nystatin, ketoconazole, miconazol, etc.), antibiotic agents (penicillins, cephalosporins, erythromycin, tetracycline, aminoglycosides, etc.), antiviral agents (e.g, acyclovir, idoxuridine, etc.), breath fresheners (e.g. chlorophyll), antitussive agents (e.g., dextromethorphan hydrochloride), anti-cariogenic compounds (e.g., metallic salts of fluoride, sodium monofluorophosphate, stannous fluoride, amine fluorides), analgesic agents (e.g., methylsalicylate, salicylic acid, etc.), local anesthetics (e.g., benzocaine), oral antiseptics (e.g., chlorhexidine and salts thereof, hexylresorcinol, dequalinium chloride, cetylpyridinium chloride), anti-inflammatory agents (e.g., dexamethasone, betamethasone, prednisone, prednisolone, triamcinolone, hydrocortisone, etc.), hormonal agents (oestriol), antiplaque agents (e.g, chlorhexidine and salts thereof, octenidine, and mixtures of thymol, menthol, methysalicylate, eucalyptol), acidity reducing agents (e.g., buffering agents such as potassium phosphate dibasic, calcium carbonate, sodium bicarbonate, sodium and potassium hydroxide, etc.), and tooth desensitizers (e.g., potassium nitrate). This list is not meant to be exclusive. The solid formulations of the invention may also include other locally active agents, such as flavorants and sweeteners. Generally any flavoring or food additive such as those described in Chemicals Used in Food Processing, pub 1274 by the National Academy of Sciences, pages 63-258 may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.